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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/620,333	VOYTA ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-11 and 14-45* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-11,14-33 and 39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 9/26/06, is acknowledged and has been entered. Claims 1, 4-6, 8-9, 11, 15-16, 18-21, 27, 29-30, 41-42, and 44 have been amended. Claims 7 and 12-13 were canceled. Claims 1-6, 8-11, 14-45 are pending in the application, with claims 34-38 currently withdrawn.

Election/Restrictions

2. Applicant's affirmation of the election with traverse of **Group I, claims 1-33 and 39-45,** and of the species of **nucleic acid** in the reply filed on 9/26/06 is acknowledged. The traversal is on the ground(s) that search and examination of all pending claims would not pose an undue burden on the examiner. This is not found persuasive because as set forth in the previous Office action, the inventions of Group I and Group II are patentably distinct and would require non-coextensive searches. For example, a search of the composition claims would require a separate structure search as well as different patentability considerations. Regarding the requirement for the election of species, a search of the prior art relating to nucleic acid array art would not necessarily uncover art relating to protein or antibody arrays (for example), and therefore separate searches would be required, presenting an undue burden. In addition, different considerations would arise in determining the patentability of the claimed methods under 112, 1st paragraph for protein vs. nucleic acid arrays. As such, a search of all pending claims and species would represent an undue burden of search and examination.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 34-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/26/06.

Terminal Disclaimer

4. The terminal disclaimer filed on 9/26/06 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of **10/620,332** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Rejections/Objections Withdrawn

5. The provisional rejections of claims 1-33 and 39-45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/620,332 are withdrawn in light of the above-mentioned terminal disclaimed filed on 9/26/06.

6. The objections to the specification as failing to provide antecedent basis for claimed subject matter are withdrawn in response to Applicant's amendments to the specification (see Applicant's reply, p. 2).

7. The objections to claims 1, 6-7, 9, 11, 27, 29-30, 40, and 44 have been withdrawn in view of the claim amendments and in light of the cancellation of claim 6.

8. The rejections under 112, 2nd paragraph not reiterated below have been withdrawn.

Priority

9. The first paragraph of the specification identifies the instant application as being "related" to copending applications 10/046,730 and 10/462,742, and to application 10/050,188 (now US 6,905,826). It is unclear whether Applicant intends to claim benefit under 35 USC 120 to these applications by this reference. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. **For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.**

Instructions for perfecting benefit claims under 35 USC 120 are detailed further in the previous Office action (see p. 5-6).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-6, 8-11, 14-33 and 39-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 1 is indefinite because it is unclear whether the solid support actually includes probes bound to the enzyme conjugates or not. The claim recites that at least some of the

plurality of probes **are bound** to the enzyme conjugates, which suggests that the support is provided with probes that are already bound to the enzyme conjugates.

However, dependent claims 11 and 19-22 recite methods according to claim 1 in which the support is contacted with a sample that includes *target molecules labeled with the enzymes* (i.e., the enzyme conjugates are present in the sample). In these claims, the binding of the enzyme conjugates to the probes appears to be an active method step that occurs during the performance of the methods. For example, claim 11 recites "contacting the support surface" with a sample that includes the first and second enzyme conjugates, yet the support surface that is being referred to (that of claim 1) already has probes bound to enzyme conjugates disposed on the surface layer according to claim 1. It appears that the dependent claims recite method steps that occur before those of claim 1, but this is not clearly recited in the claims.

The claims are indefinite and confusing because it is unclear when the probes become bound to the enzyme conjugates, and in particular whether the probes/enzyme conjugates are actually bound to the solid support of claim 1.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 3-6, 9-11, 15-26, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. (US 4,931,223) in view of Fodor et al. (US 6,309,822 B1).

Bronstein et al. teach a method of detecting chemiluminescent emissions on a solid support (coated matrix such as a nylon membrane), comprising contacting a surface layer of the solid support with a substrate composition that is a mixture of two or more enzymatically cleavable chemiluminescent substrates that are capable of being activated (cleaved) by different enzymes (see in particular the abstract; column 1, line 53 to column 3, line 3; column 7, lines 5-19; column 8, lines 1-21; Examples I-II; and claim 17 in particular). The signals produced by the two chemiluminescent substrates are then detected either simultaneously or sequentially (column 2, line 11; column 8, lines 16-21 and 42-65; column 11, lines 3-19). Bronstein et al. further teach that a plurality of probes may be immobilized in discrete areas ("spots") on the solid support (see column 8, lines 1-7; column 10, lines 29-36; column 11, lines 15-18; column 13, lines 5-18). The probes may be capture antibodies as in Example I or nucleic acid probes as in Example II (see also column 2, line 64 to column 3, line 3). At least some of the probes are bound to a first enzyme conjugate comprising the first enzyme, and at least some of the probes are bound to a second enzyme conjugate comprising the second enzyme (see the above passages and especially column 8, lines 1-21).

Bronstein et al. fail to specifically teach that the plurality of probes are immobilized in the discrete areas at a density of at least 50 discrete areas per cm2.

Fodor et al. teach high density probe arrays, in which greater than about 400,000 different probes can be immobilized per cm2 (see in particular the abstract; column 2, lines 33-43; column 3, lines 18-48). The high-density probe arrays can be used to detect and quantify target nucleic acid sequences and/or to monitor the expression of a multiplicity of genes (column 33, lines 20-31; column 5, lines 34-36; column 2, lines 53-61). Fodor et al. teach that the high density probe arrays offer several advantages, including reduced intra- and inter-array variability, increased information content, and higher signal-to-noise ratio (see column 12 to column 15, line 60). In particular, Fodor et al. note that the arrays have advantages over blotted arrays (which is the technique used in Bronstein et al.), such as significantly higher hybridization efficiencies (column 14, line 61 to column 15, line 12).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the high density probe arrays of Fodor et al. as the solid support in the method of detecting chemiluminescent emissions of Bronstein et al. in order to allow for increased information content and massively parallel processing of hybridization data, reduction of assay variability, and/or to detect and quantify a multiplicity of genes with increased information content and sensitivity.

One would have a reasonable expectation of success in using the solid support of Fodor et al. in the method of detecting chemiluminescent emissions of Bronstein et al. because Fodor et al. teach that the microarrays may be used in methods employing chemiluminescent detection (column 49, lines 5-12, column 82, lines 43-65) and also that enzyme labels may be used

(column 20, lines 51-61). One would also have a reasonable expectation of success because Fodor et al. teach that the solid support may be a nylon membrane (column 95, lines 49-57), which is the same material used as the solid support by Bronstein et al. One would also have a reasonable expectation of success because Bronstein et al. teach that the chemiluminescent detection method can be used in any art-recognized immunoassay, chemical assay, or nucleic acid probe assay technique (column 2, lines 54-68).

With respect to claims 3-6, Fodor et al. teach that in addition to test probes, the array can include control probes or normalization controls, which can serve to calculate a background signal and to allow for quantification of unknowns, or as expression level controls (column 14, lines 28-35; column 4, lines 6-12; column 9, lines 6-46; column 19, lines 14-21; column 22, line 57 to column 24, line 39; and column 35, line 29 to column 36, line 61). The control probes can be localized at any position in the array or at multiple positions throughout the array (column 23, lines 20-23). The intensity of the second (unknown) signal is quantified by comparing the signal intensity to that of mismatch control and/or background signal intensity (column 24, lines 9-15; column 26, lines 10-25). The signals are detected by detecting the signal strength at each location (representing a different probe) on the array (column 35, lines 29-44).

With respect to claim 9, Bronstein et al. teach detecting the location of the signals on the solid support in that the brightness of the spots are visualized (see for example column 11, lines 15-19).

With respect to claim 10, Bronstein et al. teach nucleic acid probes (column 2, line 64 to column 3, line 3).

With respect to claim 11, Bronstein et al. teach contacting the solid support with a solution containing first target molecules labeled with the first enzyme (anti-beta-HCG antibodies conjugated to alkaline phosphatase) and second target molecules labeled with the second enzyme (anti-HLH antibodies conjugated to carboxylesterase) (Example I).

Fodor et al. also teach samples comprising target nucleic acids, in which the targets may be labeled with enzymes (column 20, line 28 to column 21, line 24). Different targets may be labeled with different labels (column 81, lines 16-38). Fodor et al. teach that enzyme labels may be added to the target molecules prior to or after hybridizing with the immobilized probes--i.e., that the enzyme labels may be "direct" or "indirect" labels (column 20, line 51 to column 21, line 24). For example, Fodor et al. teach that target nucleic acids may be biotinylated, which allows them to be subsequently labeled with an avidin-conjugated label after the target nucleic acids are hybridized to the probes. As such, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules since Fodor et al. teach that both indirect and direct labeling are effective means of labeling target molecules.

With respect to claim 14, Fodor et al. teach that the target molecules may be pools of nucleic acids (column 2, line 62 to column 6, line 9). For example, the sample may comprise a first pool (total RNA pool) that is mixed or spiked with a second pool of 13 target RNAs (see column 103, line 45 to column 104, line 8). As another example, a sample including target pool of nucleic acids can be used together or "spiked" with a second pool of control nucleic acids (column 24, lines 22-39; column 9, lines 35-41; column 6, lines 36-63).

With respect to claims 15-16, Fodor et al. teach that the target nucleic acid sample may comprise mRNA transcripts or nucleic acids derived from mRNA transcripts, such as cDNA

derived (reversed transcribed) from mRNA (column 17, line 47 to column 18, line 34; column 18, lines 35-54).

With respect to claim 17, Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene (column 18, lines 9-34).

With respect to claims 18-22, Fodor et al. teach control probes as discussed above with respect to claim 3, and both Bronstein et al. and Fodor et al. each teach samples comprising target nucleic acids, in which the targets may be labeled with different enzymes as discussed above with respect to claims 11 and 13. The sample of Fodor et al. may include pools of nucleic acids that are mRNA transcripts or nucleic acids derived from mRNAs such as cDNA discussed above with respect to claim 14. Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene as discussed above with respect to claim 17.

With respect to claims 23-26, Fodor et al. teach arrays with densities of 400,000 per cm2.

With respect to claims 28-29, Bronstein et al. teach that the first and second chemiluminescent substrates emit light of different wavelengths (see for example the abstract), and that the signals are imaged using multiple filters that isolate the different signals from each of the chemiluminescent substrates (column 13, lines 43-52; column 8, lines 16-21).

With respect to claims 30 and 32, Bronstein et al. teach that the composition comprising the two chemiluminescent substrates includes carbonate buffer (see column 10, lines 48-54) and further that the chemiluminescent substrates are both 1,2-dioxetanes (see for example the abstract).

With respect to claim 31, Bronstein et al. teach a wash step prior to addition of the substrate composition (column 10, line 59 to column 11, line 2; column 13, lines 36-39).

4. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 6 above, and further in view of Ferea et al. (US 6,905,826).

Bronstein et al. and Fodor et al. are as discussed above, which teach control probes, but which fail to specifically teach that the control probes are located in one or more of the same discrete areas as probes for a target molecule.

Ferea et al. teach methods for detecting target molecules in a sample using microarrays, and in particular, controls to be used in such methods in order to allow for correction of irregularities in the shape, size, and intensity of microarray features (column 5, lines 49-52). Control signals can also be used to quantify the experimental signal (column 6, lines 16-19). Control oligonucleotide probes may be deposited onto the array in the same discrete areas ('features') as the experimental probes in order to serve as hybridization controls (column 6, lines 41-60; claim 1 and Figure 4 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art to employ control probes located in the same discrete areas as the experimental probes as taught by Ferea et al. in the method of detecting chemiluminescent emissions of Bronstein et al. and Fodor et al. in order to act as an experimental control to determine whether hybridization is occurring. One would have a reasonable expectation of success because Ferea et al. relates to methods of

detection based on nucleic acid hybridization using microarrays, which is the same format of Fodor et al.

5. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claims 11 and 14 above, and further in view of Akhavan-Tafti et al. (US 6,068,979, Applicant's Information Disclosure Statement of 8/28/03).

Bronstein et al. and Fodor et al. are as discussed above, which teach samples comprising targets that may be pools of nucleic acids and that may be labeled with enzymes. Fodor et al. also teaches indirect labeling of the targets, for example by labeling of the targets with biotin (see especially column 1, lines 3-24). However, the references fail to specifically teach that the target molecules are indirectly labeled with *digoxigenin* or that the enzyme conjugates are *antidigoxigenin:enzyme* conjugates.

Akhavan-Tafti et al. teach binding pairs, including antigen-antibody and biotin-avidin or streptavidin interaction that may be used in labeling molecules with enzymes for chemiluminescent detection. One member of a binding pair may be attached to an enzyme in order to form an enzyme conjugate, which is then capable of interacting with a target molecule labeled with the other member of the binding pair (column 4, lines 30-40 and column 5, lines 18-28). Specific examples of antigen-antibody binding pairs include antidigoxigenin-digoxigenin, where antidigoxigenin-enzyme conjugates are used as the enzyme conjugate (columns 15-16, Example 2, and Figure 3).

Therefore, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules with digoxigenin followed by labeling with an antidigoxigenin-enzyme

conjugate as taught by Akhavan-Tafti et al. in the method of Bronstein et al. and Fodor et al. because Akhavan-Tafti et al. teach that both biotin-avidin (taught in Fodor et al.) and the digoxigenin-antidigoxigenin are binding pairs that can be used for indirectly labeling nucleic acids, which is the same purpose for which the biotin-avidin system is used in Fodor et al. It would have been further obvious to employ the digoxigenin-antidigoxigenin system of Akhavan-Tafti et al. in order to label the pool of target nucleic acids that are cDNA since cDNA is one type of nucleic acid sample that may be indirectly labeled and detected in Fodor et al. (see column 17, line 56 to column 18, line 8).

One would have a reasonable expectation of success because Fodor et al. teaches indirect labeling generically; although Fodor et al. provide the example of biotin-avidin, there is no indication that the indirect labeling is intended to be restricted to this binding pair. One would also have a reasonable expectation of success because both Akhavan-Tafti et al. and Fodor et al. teach indirect labeling of nucleic acids with labels that may be enzymes.

6. Claims 2, 39-40, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 1 above, and further in view of Voyta et al. (US 5,145,772, Applicant's Information Disclosure Statement of 8/28/03).

Bronstein et al. and Fodor et al. are as discussed above, which teach a method of detecting chemiluminescent emissions on a solid support using a two-substrate composition, but which fail to specifically teach that the two-substrate composition is contacted with the solid support in the presence of a *composition comprising a chemiluminescent quantum yield enhancing material.*

Voyta et al. teach that enhancement agents such as BSA, polymeric quaternary onium (amm**onium**) salts (e.g. poly(vinyl-benzyltrimethylammonium) chloride, polyvinyl alcohol, and globular proteins act as enhancement agents in chemiluminescent assays by stabilizing light-emitting fluorophores, allowing for greater signal intensity (see the abstract; column 2, lines 45-64; column 5, line 17 to column 6, line 45; and Table I in particular). Voyta et al. teach that the enhancement agent may be simply added to the chemiluminescent substrate composition (column 13, lines 10-17), such that the chemiluminescent substrate composition would be contacted with the solid support in the presence of the enhancement agent. Other water-soluble oligomeric, homopolymeric, and copolymeric materials can be used as enhancers in addition to or instead of quaternary ammonium polymers (column 5, line 65 to column 6, line 45). These include polyacids and salts thereof, polyvinyl alcohol, and synthetic polypeptides.

Therefore, it would have been obvious to include an enhancement agent such as a quaternary onium polymer at the same time the two-substrate composition is contacted with the sample (and therefore with the solid support) as taught by Voyta in the method of detecting chemiluminescent emissions of Bronstein et al. and Fodor et al. in order to enhance the chemiluminescent signals.

With respect to claim 39, it would have been further obvious to include BSA as an additive because Voyta et al. teach that these compounds, like quaternary onium polymers, also serve to enhance the chemiluminescent signal. It would have been similarly obvious to further include polyvinyl alcohol (which is both an alcohol and a polyol) because Voyta et al. teach that this may be additionally used along with quaternary ammonium salts (see column 5, line 65 to column 6, line 23).

With respect to claim 40, Voyta et al. teach that the polymeric enhancer substances also include a counterion moiety such as halide, sulfate, arylsulfonate, alkylfulfonate, and combinations thereof (see in particular column 4, right column, the structure and line 64 to column 5, line 10).

With respect to claims 44-45, the compound poly(vinyl-benzyltrimethylammonium) chloride taught by Voyta et al. is an onium copolymer ("poly") as well as a poly(vinylbenzylammonium) salt.

7. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 1 above, and further in view of Oldham et al. (US 6,970,240 B2).

Bronstein et al. and Fodor et al. are as discussed above, which teach a method of detecting chemiluminescent emissions on a solid support (microarray), but which fail to specifically teach that the support surface further comprises a fluorescent control.

Oldham et al. teaches an apparatus for imaging an array using fluorescent or chemiluminescent detection (column 1, lines 1-58). In particular, Oldham et al. teach that at least some of the discrete areas ("feature") of the solid support (sample tile 42) may include a fluorescent marker (see also column 2, lines 18-58). The fluorescent signals generated allow for auto-focusing of the array, to allow for the size and shape of each feature in the array to be easily determined, and to normalize the chemiluminescent signals (column 3, line 55 to column 4, line 32). A normalizing fluorescent image is first collected, followed by detection of chemiluminescent signals (column 7, line 20 to column 8, line 51).

Therefore, it would have been obvious to one of ordinary skill in the art to include a fluorescent marker in the microarray solid support of Fodor et al. in order to allow for normalization of chemiluminescent signals. One would have a reasonable expectation of success because Oldham et al. teach that the apparatus is intended to be used in detection methods using nucleic acid microarrays and chemiluminescent signals, which describes the method of Bronstein et al. and Fodor et al.

8. Claims 1, 9-10, 23-26, 28-29, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bers et al. (UK Patent Application GB 2 246 197 A, published 1/22/92) in view of Fodor et al.

Bers et al. teach a method of detecting chemiluminescent emissions on a solid support, where a plurality of probes ("macromolecular species" 12) are immobilized in a plurality of discrete areas (e.g. a "planar array", see claim 9) on a surface layer of the solid support, and where at least some of the probes are bound to a label 13 that may be an enzyme such as alkaline phosphatase (see in particular the abstract; Figure 1; p. 3, line 32 to p. 4, line 35; p. 9, lines 1-3; p. 10, lines 7-18). The immobilized probes may comprise different types or groups that are each bound to distinct enzyme labels (see p. 3, line 32 to p. 4, line 11 and claims 3 and 7 in particular). Chemiluminescent emissions are detected by contacting the solid support with a mixture of a plurality of chemiluminescent substrates, where each substrate is activated ("induced") by one of the distinct enzyme labels to undergo chemiluminescent reaction (ibid and p. 7, lines 3-9). The signals are then detected using a phosphor screen. The solid support 11 may be a nitrocellulose or nylon membrane, coated glass, or a plastic microtiter plate (p. 8, lines 20-24).

Bers et al. fail to specifically teach that the probes are immobilized in discrete areas *at a density of at least 50 discrete areas per cm2.*

Fodor et al. (as discussed above) teach high density probe arrays, in which greater than about 400,000 different probes can be immobilized per cm2 (see in particular the abstract; column 2, lines 33-43; column 3, lines 18-48). The high density probe arrays can be used to detect and quantify target nucleic acid sequences and/or to monitor the expression of a multiplicity of genes (column 5, lines 34-36; column 2, lines 53-61). Fodor et al. teach that the high density probe arrays offer several advantages, including reduced intra- and inter-array variability, increased information content, and higher signal-to-noise ratio (see column 12 to column 15, line 60). In particular, Fodor et al. note that the arrays have advantages over blotted arrays (which is the technique used in the Example of Bers et al.), such as significantly higher hybridization efficiencies (column 14, line 61 to column 15, line 12).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the high density probe arrays of Fodor et al. as the solid support in the method of detecting chemiluminescent emissions of Bers et al. in order to allow for massively parallel processing of hybridizations, and/or to detect and quantify a multiplicity of genes with increased information content and sensitivity.

One would have a reasonable expectation of success in using the solid support of Fodor et al. in the method of detecting chemiluminescent emissions of Bers et al. because Fodor et al. teach that the microarrays may be used in methods employing chemiluminescent detection (column 49, lines 5-12, column 82, lines 43-65) and also that enzyme labels may be used (column 20, lines 51-61). One would also have a reasonable expectation of success because

Fodor et al. teach that the solid support may be a nylon membrane (column 95, lines 49-57), which is an example of material taught by Bers et al. One would also have a reasonable expectation of success because Bers et al. teach that the chemiluminescent detection method can be applied to a wide range of assays (p. 19, lines 32-36).

With respect to claim 9, Bers et al. teach that the detection procedure provides localized information and can be used to image spatial arrays of macromolecules (p. 8, lines 7-12).

With respect to claim 10, the probes may be nucleic acid molecules (the abstract; p. 8, line 34 to p. 9, line 3; p. 7, lines 20-22).

With respect to claims 23-26, Fodor et al. teach arrays with densities of 400,000 per cm2.

With respect to claims 28-29, Bers et al. teach that two chemiluminescent substrates may be used that have different emission maxima (p. 6, lines 30 to p. 7, line 2) and that that filters may be used in order to discriminate the different signals (p. 7, lines 3-16).

With respect to claims 32-33, Bers et al. teach that 1,2-dioxetanes and/or luminol may be used as chemiluminescent substrates in the mixture, and also that any known chemiluminescent reaction may be utilized (p. 4, lines 12-31; p. 6, lines 30-36).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-6, 8-11, 14-33 and 39-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-47 of copending Application No. 10/462,742 in view of Akhavan-Tafti (US 6,068,979) and Bronstein et al.

Although the conflicting claims are not identical, Application No. 10/462,742 also claims a method of detecting chemiluminescent emissions on a solid support, including the steps of contacting a surface layer of the solid support with a composition comprising a chemiluminescent substrate capable of being cleaved by an enzyme to produce chemiluminescence; and detecting chemiluminescent emissions on the solid support (claim 28). Application No. 10/462,742 further recites that a plurality of probes are disposed in a plurality of discrete areas on the surface layer at a density of at least 50 discrete areas per cm2. At least some of the probes are bound to an enzyme conjugate comprising an enzyme capable of cleaving the chemiluminescent substrate (claim 28)

Application No. 10/462,742 fails to recite a method in which the solid support is contacted with a *second substrate composition* capable of being cleaved by a *second enzyme* that

is provided as a *second enzyme conjugate* bound to some of the probes on the solid support, and in which both these first and second chemiluminescent signals are detected.

However, Akhavan-Tafti et al. teach a method of detecting chemiluminescent emissions on a solid support using two chemiluminescent substrates paired with two different enzymes capable of activating the two substrates, in which signals are detected from both the first and second substrates on the support (see in particular the abstract; column 1, lines 55-59; column 2, lines 38-64). Akhavan-Tafti et al. teach that using multiple substrates and multiple enzymes allows for multiple analytes in a sample to be detected in a single assay on the same support (blot). Bronstein et al. teach that in methods employing multiple chemiluminescent substrates for detection of multiple targets, the substrates may be combined as a mixture and added together (see Examples 1-2 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art to include a second chemiluminescent substrate capable of being cleaved by a second enzyme and to detect the signal from this second substrate in the method of Application No. 10/462,742 because Akhavan-Tafti et al. teach that application and detection of multiple chemiluminescent reagents to a single support allows for detection of multiple analytes in a sample. It would have been further obvious to provide the two substrates as a mixture as taught by Bronstein et al. for simplicity and to reduce the number of operational steps.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

12. Applicant's arguments filed 9/26/06 have been fully considered.

13. With respect to the rejection of the claims under 112, 2nd paragraph as being indefinite as to whether the solid support includes probes bound to the enzyme conjugates or not (see the previous Office action at p. 9, item 12), Applicant's reply asserts that the claim amendments have addressed the rejections (see p. 12), to which the Examiner disagrees. Claim 1 conveys that the solid support includes probes that are bound to enzyme conjugates, while the dependent claims appear to set forth process steps in which the probes on the support are contacted with and become bound to the enzyme conjugates. As such, the claims are indefinite because it is unclear whether the solid support of claim 1 is provided with probes bound to the enzyme conjugates, or alternatively whether this occurs during the performance of the method.

14. With respect to the rejections under 35 USC 103(a) as being unpatentable over Bronstein in view of Fodor, as well as over Bers in view of Fodor, Applicant's arguments (see p. 12-14) have been fully considered but they are not persuasive. Applicant argues that although Fodor teaches chemiluminescent detection as well as the use of enzyme labels, the reference fails to specifically teach the use of enzyme labels together with chemiluminescent detection (see especially Applicant's reply at p. 13).

This argument is not persuasive because it amounts to a piecemeal analysis of the references; however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, the relevant teaching of the use of enzyme labels together with chemiluminescent detection is found in Bronstein (see especially the previous Office action at p.

11-12). Similarly, the rejections over Bers in view of Fodor, the Bers reference was relied upon for this teaching (see especially p. 21-22 of the previous Office action). Rather, the Fodor reference was relied upon for its teaching of high-density arrays. The examiner made mention of the fact that Fodor also teaches the use of enzyme labels, as well as chemiluminescent detection, in the context of demonstrating that one skilled in the art would have a reasonable expectation of success in combining the reference teachings.

Applicant further argues (see p. 13) that one of ordinary skill in the art would not have been motivated to modify the reference teachings in order to arrive at the claimed invention, specifically because one skilled in the art would have expected the chemiluminescent species to migrate during the assay, thereby reducing spatial resolution and resulting in inaccurate assay data (see p. 13). This is not found persuasive because the evidence of record establishes that it was well known in the art to employ chemiluminescent detection on solid supports (see especially the Bronstein et al. and Bers references). See also Tonkinson ("Chemiluminescent Detection of Immobilized Nucleic Acids--From Southern Blots to Microarrays". In: Luminescence Biotechnology: Instruments and Applications, Edited by Van Dyke et al., CRC Press: Boca Raton, FL, 2002), cited in the previous Office action, especially at p. 196-199), which shows that chemiluminescent detection on high-density arrays was known in the art at the time of the invention.

Moreover, Applicant has not established a nexus between the merits of the invention and the asserted secondary considerations of unexpected results. Furthermore, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(c).

In conclusion, although the statements in the specification regarding migration of enzyme labels have been duly evaluated, it is maintained that the preponderance of the evidence of record supports a determination of obviousness rather than of non-obviousness.

15. Regarding the rejections on the grounds of non-statutory obviousness-type double patenting, the terminal disclaimer filed on 9/26/06 is persuasive to overcome the rejections over copending application No. 10/620,332. Applicant's reply states that the terminal disclaimer also relates to copending application No. 10/462,742 (see the reply p. 14-15); however, the terminal disclaimer does not mention application No. 10/462,742, and therefore, the rejections over this second application are maintained for the reasons set forth above.

Conclusion

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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